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EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Acting Director General

Brussels,
SANTE/E3/LF/np

Subject: Request for information

In your letter dated 16 March 2015 you ask me to send you a copy of a "non-published EU report" on endocrine disruptors, which was referred to in an article in the journal The Guardian.

We have no clear indication what "non-published EU report" the newspaper article refers to. To date, the Commission (as College) has not adopted any paper in this respect. We can only assume that the newspaper article refers to drafts prepared by individual Commission departments for internal discussions.

DG SANTE is only aware of one such draft which is available on CIRCABC (https://circabc.europa.eu/sd/a/7c338c57-2b2a-4324-a8c0-b7f074b51a54/02_Revised%20version%20of%20elements%20for%20criteria(0).pdf) and which is also attached as an annex to this letter for your convenience.

Yours sincerely,

For the Director General absent,
Martin SEYCHELL
Deputy Director General

Ladislav Miko

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EUROPEAN COMMISSION
DIRECTORATE-GENERAL
ENVIRONMENT

Directorate D - Water, Marine Environment & Chemicals
ENV.D.3 – Chemicals, Biocides and Nanomaterials

Brussels, 19 February 2013
ED-AD-HOC-6/2013/02

THE COMMUNITY STRATEGY FOR ENDOCRINE DISRUPTORS

6TH AD HOC MEETING OF

COMMISSION SERVICES, EU AGENCIES AND MEMBER STATES

Centre de Conférence A. Borschette, room 1A, rue Froissart 36, Brussels
20 February 2013 (09:30 – 17:30)

Concerns: **Brainstorming and discussion on the criteria for Endocrine Disruptors**

Agenda Point: **5**

Action Requested: **A paper setting out possible elements for the definition, identification and categorisation of endocrine disruptors was developed by DG ENV at the end of 2012 and presented to the 4th meeting of the expert advisory group and to the 5th ad hoc meeting of Commission Services, EU agencies and member states (meeting document ED-AD-HOC-5/2012/04). The members of both groups were asked to provide written comments by 7 January 2013.**

A draft final report of ED expert advisory group on criteria for EDs was discussed at their meeting on 4-5 February 2013.

This document contains a revised version of possible elements for criteria for identification of endocrine disruptors based on the comments received and the draft report of ED expert advisory group.

During the ad-hoc meeting the revised version of possible elements for ED criteria as currently considered by DG ENV will be presented and the ad-hoc group may wish to provide comments.

The participants to the meeting are invited to:

- take note of this document and provide comments

Revised version of possible elements for criteria for identification of endocrine disruptors (clean version)

1. Definition

An *endocrine disruptor* is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations. (WHO/IPCS)

2. Categories of Endocrine Disruptors

For the purpose of categorisation for endocrine disruption, substances are allocated to one of two categories based on strength of evidence and additional considerations in weight of evidence.

Categories for endocrine disruptors

- Category 1: Endocrine disruptors
- Category 2: Suspected endocrine disruptors

3. Criteria for Placing Substances in Categories

Category 1 –Endocrine disruptors

Substances are placed in category 1 when they are known to have caused endocrine mediated adverse effects in humans or population relevant effects on animal species living in the environment or when there is evidence from experimental studies, possibly supplemented with other information (e.g. in vitro, in silico, read across), to provide a strong presumption that the substance has the capacity to cause endocrine mediated adverse effects in humans or population relevant effects on animal species living in the environment.

The experimental studies shall provide clear evidence of endocrine-mediated adverse effects in the absence of other toxic effects, or if occurring together with other toxic effects, the endocrine-mediated adverse effects should be considered not to be a secondary non-specific consequence of other toxic effects.

However, when there is (e.g. mechanistic) information demonstrating that the effects are clearly not relevant for humans and population of animal species living in the environment, category 2 may be more appropriate.

Substances can be allocated to the category 1 based on:

- Evidence from humans or from animal species living in the environment where it is plausible that the observed adverse effect is endocrine-mediated, or
- Experimental studies where it is plausible that the observed adverse effects are caused by an endocrine mode of action, or

- Experimental animal studies showing an endocrine activity *in vivo* which is clearly linked to adverse effects *in vivo* (e.g. through read-across).

Category 2 – Suspected endocrine disruptors

Substances are placed in category 2 when there is some evidence for endocrine mediated adverse effects from humans, animal species living in the environment or experimental animals, and where the evidence is not sufficiently strong to place the substance in category 1. If, for example, limitations in the study (or studies) make the quality of evidence less convincing, category 2 could be more appropriate.

These endocrine disrupting effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the endocrine mediated effect should be considered not to be a secondary non-specific consequence of other toxic effects.

Substances can be allocated to this category based on:

- Evidence from humans or from animal species living in the environment where it is suspected that the observed adverse effect is endocrine-mediated, or

- Experimental studies where it is plausible that the observed adverse effects are caused by an endocrine mode of action but that specific weaknesses in study design or execution weaken this conclusion, or

- Experimental studies where it is suspected that the observed adverse effects are caused by an ED mode of action, or

- Experimental animal studies showing endocrine activity *in vivo* which is suspected to be linked to adverse affects *in vivo* (e.g. through read-across), or

- *in vitro* studies showing endocrine activity, combined with toxicokinetic *in vivo* data which is suspected to be linked to adverse effects *in vivo* (e.g. through read-across, chemical categorisation and QSAR predictions).

4. Additional considerations

4.1 Endocrine system

- No need for defining the endocrine system
    - Scientific terms are usually not defined;
    - Very little is known about endocrine system of invertebrates and thus difficult to develop a good definition;

- If the definition would be desired, then one suitable definition might be: ‘The endocrine system is a system regulating all biological processes in the body by synthesising chemical messengers (hormones) in one tissue which are transported (by the circulatory system) to other tissues in which they produce their physiological effects’

4.2 Route of exposure

- No need for specifying route of exposure here, but might be useful to address it in the guidance document; (for determination of endocrine activity all route of exposure are used, while for determination of adverse effects physiological route of exposure is used)

4.3 Adversity

- It might be useful to define the adversity in the definition section
- WHO/IPCS 2009 definition seems to be suitable: A change in the morphology, physiology, growth, reproduction, development or lifespan of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of capacity to compensate for additional stress or an increase in susceptibility to other influences.

4.4 Mode of action

- It might be useful to define the mode of action, however, there is no readily available definition;
- One possibly suitable defines MoA as: The biologically plausible sequence of key events, starting with the interaction of an agent with a cell, through functional and anatomical changes leading to an observed effect.
- Authors of this paper need additional considerations on whether and how to incorporate it in the criteria

4.5 Proof of causality

- It should be addressed but no need for additional elaboration as it is already covered in the criteria

4.6 Data

- It seems to be useful to describe in general terms data to be used for the assessment; Possible description is as follow: Categorisation of a substance for endocrine disruption is made on the basis of evidence from reliable and acceptable studies. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data.

4.7 Potency

- No potency consideration
    - It is not relevant for the hazard identification;
    - Potency on its own does not inform for high/low concern; potency makes sense only if combined with exposure information and information on uncertainties;
    - A risk from low potent chemical can be higher than from high potent chemical if exposure to low potent is higher than to high potent chemical;
    - There is no scientific way how to define the cut-off threshold; it is always decision based on impacts;
    - Impossible to extrapolate potency cut offs across species;
    - No potency consideration for CMRs classes;
    - It has been argued that majority of effects seen for endocrine disruptors would be also identified as carcinogenicity or toxic to reproduction; if a threshold would be

established for endocrine disruption, then it could happen that a substance would not be identified as an endocrine disruptor even if it is a carcinogen or toxic to reproduction and the endocrine mode of action is well known.

4.8 Lead toxicity

- It should not be considered as it is not important for hazard identification whether a substance is also causing other effect at lower concentration level;

4.9 Severity

- It should not be considered; all adverse effects are relevant;

4.10 Irreversibility

- It should not be considered; all adverse effects are relevant;

4.11 Specificity

- It should be considered
- It is incorporated in the criteria

4.12 Step by step procedure

1. Gather all available data
2. Consider adversity and mode of action in parallel
3. Assess the data quality, reliability, reproducibility and consistency
4. Evaluate specificity
5. Evaluate human and wildlife relevance
6. Final (eco)toxicological evaluation and categorisation

Revised version of possible elements for criteria for identification of endocrine disruptors (changes tracked)

1. Definition

An *endocrine disruptor* is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations. (WHO/IPCS)

~~A *suspected endocrine disruptor* is an exogenous substance or mixture that may alter function(s) of the endocrine system and consequently may cause adverse health effects in an intact organism, or its progeny, or (sub)populations. (DK)~~

~~A *potential endocrine disruptor* is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations. (WHO/IPCS)~~

2. Categories of Endocrine Disruptors

For the purpose of categorisation ~~of endocrine disruptors~~ for endocrine disruption, substances are allocated to one of ~~three~~ two categories based on ~~[weight of evidence] / [level of evidence]~~strength of evidence and additional considerations in weight of evidence.

Categories for endocrine disruptors

- Category 1: ~~Known or presumed~~ Endocrine disruptors
  - ~~Category 1a: Known endocrine disruptors~~
  - ~~Category 1b: Presumed endocrine disruptors~~
- Category 2: Suspected endocrine disruptors
- ~~Category 3: Potential endocrine disruptors~~

3. Criteria for Placing Substances in Categories

Category 1 – ~~Known or presumed~~ Endocrine disruptors

Substances are placed in category 1 when they are known to have caused endocrine ~~ED~~ mediated adverse effects in humans or ~~[animal species living in the environment] / [~~population relevant effects on animal species living in the environment ~~] / [ecosystem relevant adverse effects]~~ or when there is evidence from ~~[animal studies] / [~~experimental ~~animal~~ studies~~]~~, possibly supplemented with other information (e.g. in vitro, in silico, read across), to provide a strong presumption that the substance has the capacity to cause ~~ED~~ endocrine mediated adverse effects in humans or ~~[animals living in the environment] / [~~population relevant effects on animal species living in the environment~~] / [ecosystem relevant adverse effects]~~.

The ~~[animal studies] / [~~experimental ~~animal~~ studies~~]~~ shall provide clear evidence of endocrine~~ED~~-mediated adverse effects in the absence of other toxic effects, or if occurring together with other toxic effects, the endocrine~~ED~~-mediated adverse effects should be considered not to be a secondary non-specific consequence of other toxic effects.

However, when there is (e.g. mechanistic) information demonstrating that the effects are clearly not relevant ~~raises doubt about the relevance of the effect~~ for humans ~~or~~ and ~~[animal species living in the environment] / [~~population of animal species living in the environment~~]~~, category 2 may be more appropriate.

~~Category 1 is further divided into two sub-categories on the basis of whether the evidence for classification is primarily from human data or data from [animals living in the environment] / [field studies] (Category 1A – Known Endocrine Disruptors) or from [laboratory animal studies] / [experimental animal studies] (Category 1B – Presumed Endocrine Disruptors).~~

~~Substances can be allocated to the sub-category 1A based on evidence from humans or from [animal species living in the environment] / [field studies] where it is plausible that the observed adverse effect is endocrineED-mediated.~~

Substances can be allocated to the ~~sub-~~category 1~~B~~ based on:

- Evidence from humans or from ~~[~~animal species living in the environment~~] / [field studies]~~ where it is plausible that the observed adverse effect is endocrine-mediated, or
- ~~[Animal studies] / [~~Experimental ~~animal~~ studies~~]~~ where it is plausible that the observed adverse effects are caused by an endocrine ~~ED~~ mode of action, or
- ~~[Animal studies] / [~~Experimental animal studies~~]~~ showing an ~~ED~~ endocrine activity *in vivo* which is clearly linked to adverse effects *in vivo* (e.g. through read-across).

Category 2 – Suspected endocrine disruptors

Substances are placed in category 2 when there is some evidence for ~~ED~~ endocrine mediated adverse effects from humans, animal species living in the environment or experimental animals, and where the evidence is not sufficiently ~~convincing~~ strong to place the substance in category 1. If, for example, limitations in the study (or studies) make the quality of evidence less convincing, category 2 could be more appropriate.

These endocrine disrupting ~~Such~~ effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ~~ED~~ endocrine mediated effect should be considered not to be a secondary non-specific consequence of other toxic effects.

Substances can be allocated to this category based on:

- Evidence from humans or from animal species living in the environment where it is suspected that the observed adverse effect is endocrine-mediated, or
- Experimental studies where it is plausible that the observed adverse effects are caused by an endocrine mode of action but that specific weaknesses in study design or execution weaken this conclusion, or

- Experimental ~~animal~~ studies where it is suspected that the observed adverse effects are caused by an ED mode of action, or

- Experimental animal studies showing endocrine activity *in vivo* which is suspected to be linked to adverse affects *in vivo* (e.g. through read-across), or

- *in vitro* studies showing endocrine activity, combined with toxicokinetic *in vivo* data which is suspected to be linked to adverse effects *in vivo* (e.g. through read-across, chemical categorisation and QSAR predictions).

~~Category 3 – Potential endocrine disruptors~~

~~Substances are placed in Category 3 when there is some *in vitro/in silico* evidence indicating a potential for endocrine disruption mediated adverse effects in intact organisms and where the evidence is not sufficiently convincing to place the substance in category 1 or 2.~~

~~The evidence could also be observed effects *in vivo* where there is general but not specific evidence relating those to ED mediated adverse effects (i.e. that may, or may not, be ED-mediated).~~

4. Additional considerations

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7. Gather all available data

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9. Assess the data quality, reliability, reproducibility and consistency

10. Evaluate specificity

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10.12. Final (eco)toxicological evaluation and categorisation